ELSEVIER

European Journal of Cardio-thoracic Surgery 15 (1999) 314–319

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

Perioperative mortality and major cardio-pulmonary complications after lung surgery for non-small cell carcinoma[1]

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Received 21 September 1998; received in revised form 30 November 1998; accepted 22 December 1998

Abstract

Objectives: A database of patients operated of lung cancer was analyzed to evaluate the predictive risk factors of operative deaths and life-threatening cardiopulmonary complications. **Methods**: From 1990 to 1997, data were collected concerning 634 consecutive patients undergoing lung resection for non-small cell carcinoma in an academic medical centre and a regional hospital. Operations were managed by a team of experienced surgeons, anaesthesiologists and chest physicians. Operative mortality was defined as death within 30 days of operation and/or intra-hospital death. Respiratory failure, myocardial infarct, heart failure, pulmonary embolism and stroke were considered as major non-fatal complications. Preoperative risk factors, extent of surgery, pTNM staging, perioperative mortality and major cardio-pulmonary complications were recorded and evaluated using chi-square statistics and multivariate logistic regression. **Results**: Complete data were obtained in 621 cases. The overall operative mortality was 3.2% (n = 19). Cardiovascular complications (n = 10), haemorrhage (n = 4) and sepsis or acute lung injury (n = 5) were incriminated as the main causative factors. In addition, there were 13 life-threatening complications (2.1%) consisting in strokes (n = 4), myocardial infarcts (n = 5), pulmonary embolisms (n = 1), acute lung injury (n = 1) and respiratory failure (n = 2). Four independent predictors of operative death were identified: pneumonectomy, evidence of coronary artery disease (CAD), ASA class 3 or 4 and period 1990–93. In addition, the risk of major complications was increased in hypertensive patients and in those belonging to ASA class 3 or 4. A trend towards improved outcome was observed during the second period, from 1994 to 97. **Conclusion**: Our data demonstrate that perioperative mortality is mainly dependent on the extent of surgery, the presence of CAD and provision of adequate medical and nursing care. Preoperative testing and interventions to reduce the cardiovascular risk factors may help to further improve perioperative outcome.

Keywords: Lung resection; Primary bronchogenic lung cancer; Operative mortality

1. Introduction

Lung cancer represents a major problem, it is the most common cause of cancer death in Western countries [1]. After diagnosis, survival is poor for all treatments except when surgical resection is possible: more than 25% of operated patients will survive for 5 years [2]. Long-term prognosis is largely determined by histologic findings, the anatomic extent of the tumoural process and the completeness of the surgical resection [3,4].

Over the last decades, life expectancy in developed countries has increased far beyond 70 years. Accurate staging and the combination of neoadjuvant therapy with surgical resection meet the need to treat a large variety of patients with lung cancer, including elderly and chronically ill patients with severe pathophysiologic alterations [4].

Operative mortality ranges from 1 to 12% and is mainly

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[1] Presented at the 12th Annual Meeting of the European Association for Cardio-thoracic Surgery, Brussels, Belgium, September 20–23, 1998.

1010-7940/99/$ - see front matter
PII: S1010-7940(99)00006-8

related to the presence of intercurrent illness, to the patient's general condition, postoperative infection and uncontrolled haemorrhage [5,6]. In addition, a wide spectrum of postoperative cardiopulmonary complications may also occur in as much as 30–60% of patients [7]. Therefore, improvement of patient's survival and quality of life following lung resection can be achieved through identification of operative risk factors, accurate staging, selection of the most appropriate therapy and high quality perioperative medical care.

In this article, we report 30-day mortality, major non-fatal cardiopulmonary complications and their risk factors in 621 consecutive patients operated for lung cancer.

2. Methods

2.1. Patient selection

From January 1, 1990 to December 31, 1997, 634 consecutive patients underwent thoracic surgery for non-small cell carcinoma in two institutions: an academic medical centre (Hôpital Universitaire de Genève, HUG) and a regional hospital (Centre Valaisan de Pneumologie, CVP) that covered an area with approximately 450 000 inhabitants. All patients were operated by one of three surgeons specialized in thoracic surgery, and they were managed by the same team of experienced anaesthesiologists and chest physicians.

Preoperative evaluation included a complete history, physical examination, blood cell count, biochemical profile, chest roentgenogram, ECG, pulmonary function tests and computed tomographic scan of the chest and abdomen. Differential lung perfusion scans were performed in patients with forced expiratory volume in 1 s lower than 80% of predicted value. Patients with risk factors for coronary artery disease or with low functional capacity were further evaluated by transthoracic echocardiography, stress testing (maximal exercise or thallium-dipyridamole myocardial scintigraphy) or coronary angiogram.

2.2. Operative procedures and anaesthesia management

The operations were performed through a standard posterior-lateral or an anterior mini-thoracotomy and were divided into pneumonectomy, lobectomy, lesser resection (segmentectomy, partial or wedge resection) and explorative thoracotomy. Prophylactic antibiotic (cefuroxime 1.5 g/8 h, for 1 or 2 days) was given routinely and, after the induction of anaesthesia, a double-lumen tube was inserted for one-lung ventilation. At the end of surgery, all patients were successfully extubated and were monitored for 24–48 h in an intermediate care unit. Epidural analgesia was provided in 82% of patients, for 48–96 h after surgery. Over the last 4-year period (1994–1997), preoperative preparation and postoperative recovery program were reinforced including routine chest physiotherapy, early mobilization and oral feeding as well as more intense analgesic regimen with continuous administration of opiate and local anaesthetics.

2.3. Data collection

Data were extracted from the medical and nursing files. Retrospective review was conducted until September 1992 in one centre (CVP) and until November 1994 in the other (HUG); thereafter data were prospectively recorded. Information were gathered concerning 20 items including demographic, clinical, functional, surgical and pathological variables. Binary data were obtained by identification of the presence or absence of relevant co-morbidities. The diagnosis of coronary artery disease (CAD) was based on a positive history of myocardial infarct or angina pectoris, typical Q waves on the electrocardiogram, positive stress test or evidence of coronary artery stenosis on the angiogram. Elevated blood pressure requiring chronic antihypertensive treatment and diabetes mellitus treated with insulin or oral hypoglycaemic medications were considered significant co-morbidities. The following cut-off points were selected for age (≥ 70 years), body mass index (≥ 30), renal function (serum creatinin >160 mg/dl), pulmonary function (forced expiratory volume in 1 s, FEV_1, less than 60% of predicted values), haemoglobin level (≤ 9 g/dl in female and ≤ 10 g/dl in male) and operation duration (≥ 160 min). The 5-grade classification of the American Society Anaesthesiology (ASA) was used as a composite index of the patient's general status [8]. Lung cancer was classified according to histological diagnosis, staging (I, II, IIIa, IIIb and IV) and surgical resection. The pTNM scoring system published in 1986 by the American Joint Committee on Cancer International Classification and partially modified in 1992 was used for staging of bronchogenic tumours.

Operative mortality was defined as any death occurring within 30 days of operation or after 30 days, in patients who remained in the hospital since the time of operation.

Non-fatal life-threatening cardiopulmonary events occurring within the first 30-postoperative days were defined as major complications, if pharmacological or technical support was required, permanent disability ensued or if life expectancy was threatened. Major respiratory morbidity was considered if re-intubation and mechanical ventilation for longer than 24 h was required; acute lung injury was defined as diffuse pulmonary oedema, without cardiac causes and with low oxygenation index (PaO_2/FIO_2 lower than 300 mmHg). Pulmonary thromboembolism, heart failure (requiring the administration of vasoactive drugs), acute myocardial infarct and stroke were also recorded. Bronchopleural fistula and prolonged air-leaks were not considered.

2.4. Statistical analysis

We studied the possible contribution to mortality and major morbidity of demographic, clinical, functional, surgical and pathological variables, as well as of the operating

centre and the year of operation. In univariate analysis, the significance of each factor was evaluated using the χ^2 test for categorical variables. Most of the variables were also tested by Spearman rank (non-parametric) correlation analysis to determine whether the potential risk factors were truly independent variables. Factors with an univariate significance level of $P < 0.25$ were initially included as independent variables and multivariate logistic regression analysis was used.

3. Results

Over an 8-year period, from 1990 to 1997, complete information on all 20 items was obtained in 621 patients: 434 were operated in the academic centre (HUG) and 187 in the regional centre (CVP). There were 437 men (80%) and 184 women (20%) with a mean age of 62 years (±9, standard deviation) and 59 years (±12), respectively. Squamous cell carcinoma was the most common tumour (56%), followed by adenocarcinoma (29%), large cell carcinoma (5%) and bronchioalveolar carcinoma (4%). There was no significant time-related change in histological diagnosis, risk factors and surgical resection rate from 1990 to 1997.

For patients with resectable lung tumour, the 30-day operative mortality rate was 3.2% ($n = 19$) and cardiovascular complications ($n = 10$), haemorrhage ($n = 4$) and sepsis or acute lung injury ($n = 5$) were incriminated as the main causative factors for deaths. There were 13 life-threatening complications (2.1%) consisting in strokes ($n = 4$), myocardial infarcts ($n = 5$), pulmonary embolisms ($n = 1$), acute lung injury ($n = 1$) and respiratory failure requiring re-intubation ($n = 2$). In addition, two operative deaths (sepsis, myocardial infarct) occurred among 34 patients in whom lung resection could not been performed because of unexpected cancer extension (explorative thoracotomy).

Statistical univariate analysis demonstrated that mortality was related to the type of surgical procedure, the year of operation, the presence of CAD, ASA score and pTNM staging (Tables 1and 2). Mortality rate was increased in patients undergoing pneumonectomy (7.9%) and explorative thoracotomy (5.9%) compared with those undergoing lobectomy (1.2%) or lesser resection (2%). Gender, histological diagnosis, and surgical centre were not significantly associated with perioperative mortality. The ASA classification was correlated with the presence of CAD ($R = 0.5$, $P < 0.01$) and with chronic obstructive pulmonary disease ($R = 0.4$, $P < 0.05$). Multivariate analysis identified four independent predictors of perioperative death: pneumonectomy, CAD, ASA class 3 or 4 and period 1990–93 (Fig. 1).

For non-fatal cardiorespiratory complications, advanced age, presence of hypertension, ASA classification and year of operation (period 1990–93) were considered as significant risk factors by univariate analysis. In the final logistic regression model, the risk of major complications was increased independently during the early period 1990–93, in hypertensive patients and in those belonging to ASA class 3 or 4 (Fig. 1). All potential risk factors together accounted for 22% of the fatality rate and 18% of major cardiopulmonary complications (R^2 by multiple regression).

Table 1

Univariate analysis of preoperative risk factors for thirty-day mortality among 621 patients undergoing thoracotomy

Variable	*N*	Mortality (%)	*P*-value
Hospital			
HUG	434	3.7	n.s.
CVP	187	2.7	
Year of operation			
1990–93	288	4.8	0.06
1994–97	333	2.1	
Gender			
Male	433	3.8	n.s.
Female	188	2.0	
Age ≥ 70 years	188	3.6	n.s.
Obesity			
Body mass index ≥ 30	35	4.8	n.s.
Coronary artery disease	76	7.9	<0.01
Hypertension	188	3.9	n.s.
Arrhythmia	72	3.9	n.s.
Peripheral vascular disease	80	4.4	n.s.
Cardiac insufficiency			
NYHA class 3 and 4	38	4.2	n.s.
Diabetes mellitus	81	3.7	n.s.
Chronic obstructive pulmonary disease			
$FEV_1 \leq 60\%$ or $FEV_1/FVC \leq 60\%$	89	4.8	n.s.
Renal dysfunction			
Creatinin ≥ 160 mg/dl	17	0	n.s.
Anaemia			
(Hb < 9 for female or 10 g/dl for male)	35	0	n.s.
ASA score			
Class 3 and 4	235	6.4	<0.01

NYHA, New York Heart Association; ASA, American Society of Anesthesiology physical status; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

4. Discussion

Among 621 patients operated for non-small cell lung cancer, we found that cardiovascular, septic and haemorrhage complications were mainly implicated as causative factors in the 3.2% operative mortality rate. The risk of death was significantly increased after pneumonectomy or exploratory thoracotomy and in patients with coronary artery disease. In addition, arterial hypertension was an independent risk factor for the occurrence of life-threatening cardiopulmonary complications and a high ASA score (3–4) was a simple and valuable preoperative risk factor for an unfavourable outcome.

The overall mortality rate of 3.2% is comparable with results reported in longitudinal studies from North America and Western Europe [9–16]. However, direct comparison between studies should be interpreted cautiously due to dif-

Table 2

Univariate analysis of surgical factors and staging evaluation for 30-day mortality among 621 patients undergoing thoracotomy

Variable	*N*	Mortality (%)	*P*-value
Type of surgery			<0.05
Pneumonectomy	151	7.9	
Lobectomy	328	1.2	
Bi-lobectomy	33	3.0	
Lesser resection	75	2.7	
Exploratory thoracotomy	34	5.9	
Duration of surgery			
≥200 min	240	3.6	n.s.
PTNM Stage			<0.05
Stage I	335	1.5	
Stage II	174	4.0	
Stage IIIa	93	7.5	
Stage IIIb and IV	19	5.3	

ferences in definitions, duration of observation, type of surgery, presence of co-morbidities and referral to high-or low-volume hospitals (Table 3). In the present report, any death was reported during the 'in-hospital' and/or within '30-day after operation' and therefore yields higher mortality rate than when only considering either in-hospital or 30-day mortality.

With regard to postoperative morbidity, we believe that all complications should not be analyzed together as one group since they are not equivalent. For instance, atelectasis or myocardial ischaemia are less clinically relevant than respiratory failure, sepsis or myocardial infarct, that in turn are less clinically significant than death. Therefore, we limited our analysis to the most severe and binary perioperative outcome data, i.e. death and major cardiopulmonary complications.

In a retrospective series including 1076 consecutive patients operated between 1978 and 1984, Deslauriers et al. [11] reported 9.8% major non-fatal complications and 3.2% operative deaths that were related to higher stage of cancer, extended lung resection, advanced age, low forced expiratory volume, weigh loss and coexisting disease. In the present study, age was not considered as an independent risk factor after adjustment for concomitant morbidities. Furthermore, recent improvements in patient preparation and management have likely contributed to reduce the risk of major complications and deaths.

The extent of surgery is a well-recognized risk factor and, mortality rate ranging 3–17% following pneumonectomy and 1–10% after lesser resections have been reported (Table 3). Compared with earlier data, the main causes of deaths have now shifted from respiratory failure and bronchopleural fistula to cardiovascular disorders such as myocardial infarct, arrhythmia's and pulmonary emboli [6,11]. In addition to the extent of surgery, we identified ASA classes 3 and 4, and coronary artery disease as independent risk factors for death. Several scoring indexes have been proposed to address the severity of illness and prognostic stratification after major surgery, but few studies have dealt specifically with thoracic surgery [17]. In a prospective trial including 180 patients undergoing lung surgery, Melendez et al. [17] failed to confirm the validity of a multifactorial cardiopulmonary risk index to predict postoperative outcome. Scoring ASA physical status is commonly used for operative risk stratification by anaesthesiologists, and this simple composite index incorporates several preoperative risk factors such as age, cardiac, respiratory, renal and neurologic disorders as well as nutritional status [8].

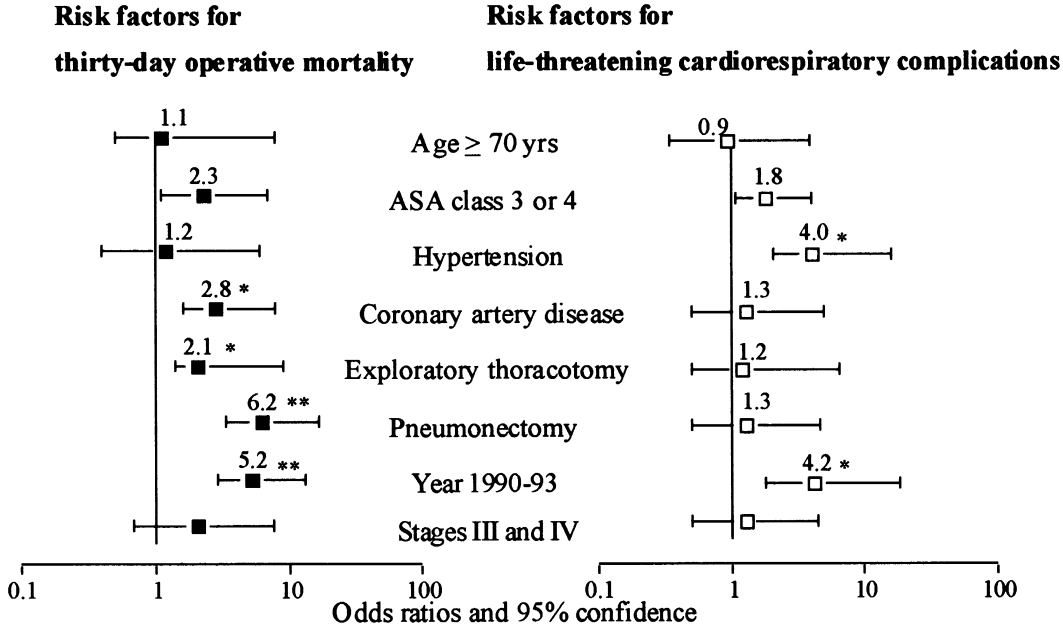

Fig. 1. Independent risk factors for operative mortality and life-threatening cardiorespiratory complications.

Table 3

Review of selected studies reporting operative mortality after lung resection for cancer

Author	Ref.	Period	Hospitals (*N*)	Patients (*N*)	Operative mortality (%)			
					Overall	Pneumon-ectomy	Lobectomy	Definition
Weiss et al.	[6]	1961–65	Multiple	547	12.4	17	9.9	30-day
Ginsberg et al.	[9]	1979–81	Multiple	2220	3.7	6.2	2.9	30-day
Kohman et al.	[10]	1972–84	Two	476	4.3	11.7	3.7	Hospital
Deslauriers et al.	[11]	1978–84	Two	1076	3.2	–	–	Hospital/30-day
Deneffe et al.	[12]	1970–85	One	720	4.7	7.9	2.9	30-day
Romano et al.	[13]	1983–86	Multiple	12439	5.0	11.6	3.9	Hospital
Kadri et al.	[14]	1980–87	One	479	5	6.8	3.9	30-day?
Damhuis et al.	[15]	1984–92	Multiple	1577	3.1	5.7	1.1	30-day
Wada et al.	[5]	1994	Multiple	7099	1.3	3.2	1.2	30-day
Roxburgh et al.	[16]	1983–96	One	179	5	6.8	2.9	Hospital
Present study	–	1990–97	Two	621	3.2	7.9	1.9	Hospital/30-day

Since CAD is a predictor of operative death and that cardiac disorders are the main causes of death, patients with cardiovascular risk factors should be screened for the presence of CAD before elective lung resection. In agreement with the guidelines of the American College of Cardiology, patients with unstable angina pectoris or recent myocardial infarct should undergo coronary catheterization, whereas a Thallium-dipyridamole myocardial scintigraphy is advocated in those patients with diabetes, peripheral vascular diseases or impaired functional status [18]. Whenever possible, in case of significant coronary artery stenosis, percutaneous angioplasty can be performed 1–2 weeks before thoracotomy or coronary artery bypass surgery can be combined at the time of lung resection or performed 2–3 weeks earlier [19].

In addition to routine investigations and the 'flight of stairs' test, measurement of the diffusing capacity to carbon monoxide (DlCO) and maximal oxygen uptake during exercise (VO_2max) have been proposed to identify those patients with low cardiopulmonary reserve capacity [20,21]. A predicted postoperative DlCO below 60% of predicted values and preoperative VO_2max below 43% of predicted values are highly predictive of postoperative cardiopulmonary complications and likely contraindicate resections involving more than one lobe. A controversial debate surrounds this issue and our data support the view that patients should not be denied surgical treatment on the exclusive basis of advanced age or a single abnormal functional test. Others have demonstrated that patients with borderline pulmonary function have minimal decrease or may even improve postoperatively, and that elderly patients could benefit from a curative surgical resection with an acceptable risk of early complications [22,23].

Interestingly, we observed lower perioperative mortality and morbidity rates during the period 1994–97 versus 1990–93, which could result from improvements in patient selection and preparation, operative techniques, and better postoperative control of pain and infection. Over recent years, there has been greater interest in lesser invasive surgical approach and better understanding of the physiologic changes associated with thoracotomy. In our group, anterior mini-thoracotomies have been performed routinely and epidural analgesic regimen have been used more frequently during the last 4 years. Although studies do not show measurable differences in pulmonary function, continuous epidural analgesia without undesirable sedation allows the patient to take deeper breaths and may decrease the risk of deep vein thrombosis and pulmonary embolism [24]. It is well recognized that preoperative pulmonary preparation, including the use of physiotherapy, exercise training, bronchodilators and antibiotic therapy can reduce the risk of postoperative infection [25].

Knowledge of risk factors for operative mortality as well as long-term survival in patients with lung cancer is useful for several reasons. First, the medical team will be able to weigh the risk of the operative procedure against the risk of death from an untreated or partially resected lesion, keeping in mind that surgery offers the only real chance of cure in non-small cell lung cancer. Second, patients considered to be at higher cardiopulmonary risk might deserve aggressive perioperative medical management including preoperative respiratory training, cardiovascular monitoring with transesophageal echocardiography and right heart catheterization, as well as a planned postoperative admission in a high-dependency unit. Alternatively, lesser invasive procedures or non-surgical alternatives could also be proposed in selected high-risk cases. Third, postoperative outcome data and assessment of their risk factor provide the basis for quality control management in a single institution and comparison of therapeutic strategies with other institutions.

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Appendix A. Conference discussion

Dr P. Kappetein (*Leiden, The Netherlands*): We did a study in almost the same period as you showed us, from 1990 to 1995, and we did it in three different centres. You also had different centres included. Did you see any difference between the centres?

Dr. de Perrot: No, we haven't seen any difference between the centres. It was the same conclusion.

Dr T. Dosios (*Athens, Greece*): You've found that coronary artery disease is one of the main risk factors for your patients. How vigorous are you in deciding which patients have coronary artery disease? Do you depend just on the history, e.g. if the patient has angina, or on his plain ECG, or do you perform an exercise test, or coronary arteriogram? How vigorous are you for checking, for examining, the coronary arteries of your patients?

Dr de Perrot: Initial assessment is based on the clinical history and ECG. If the patient gets angina, if he has arterial disease or if he has diabetes, we will do a thallium scintigraphy. If the thallium is picking up for coronary artery disease, then we will do a coronary angiography. But at first, we will do a thallium assessment.

Otherwise, if the patient has unstable angina or previous infarct of the myocardium, we will do a coronary angiography instead of a thallium scintigraphy.

Dr J Hasse (*Freiburg, Germany*): How many cases had occult coronary artery disease? If one knows about it one would take special care of the patient, monitor him more intensively and get him safely oxygenated all the time. The most dangerous thing is not to be aware of coronary artery disease. We sometimes see patients who are asymptomatic, have a normal ECG, and still have severe coronary artery disease. How many cases in your series had occult ischaemic heart disease?

Dr de Perrot: I don't exactly remember the number, but the number wasn't really high. The percentage of patients who presented with a heart problem were about ten out of the whole study. So the number of patients who had undetected coronary disease prior to surgery was really low, but I don't have the exact number.

Dr J.-F. Velly (*Pessac, France*): Do you do necropsy to assess that your patients were dead from coronary diseases?

Dr de Perrot: Yes, we have done necropsy in most of the patients who died during the operative/perioperative phase.

Dr Hasse: May I comment and ask you on a second detail of your review. You stated a mortality rate of 5.6% in the exploratory thoracotomies, which is similar to an own study, as the second highest ranking mortality behind pneumonectomy. Would you suggest that an incomplete resection instead of exploratory thoracotomy could lead to a better outcome? Have you been looking closer to those cases for the reason of a mere exploration?

Dr de Perrot: Most of these cases were exploratory thoracotomy because of the diffuse disease. In a previous series where we looked over the last 20 years, we had the same consideration, that the operative mortality in patients undergoing exploratory thoracotomy was relatively high. Therefore, this high mortality likely resulted from the extended dissection before assessment of the non-resectability of the tumour.